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PHARMACOKINETICS OF DIPHENYL METHANE DIISOCYANATE AFTER INHALATION EXPOSURE OF RATS		
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DIPHENYL METHANE DIISOCYANATE (101-68-8)		

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PHARMACOKINETICS OF MDI AFTER INHALATION

EXPOSURE OF RATS TO LABELLED MDI

Nota : A pilot study is joined to this report.

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LABORATOIRE D'ETUDES DU METABOLISME DES MEDICAMENTS
Département de Biologie
Commissariat à l'Energie Atomique
Fontenay

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CONTENTS

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LABORATOIRE D'ETUDES DU METABOLISME DES MEDICAMENTS
Département de Biologie
Centre d'Etudes de l'Energie Atomique
France

3 RESULTS

3.1 Variation in radioactivity in the blood and plasma and of the ultrafiltrab fraction after respiratory contamination with MDI (^{14}C)

3.2 Urinary and fecal excretion of radioactivity

3.3 Bile secretion of radioactivity

3.4 Autoradiography of the whole animal

3.5 Distribution in the organs

3.6 Histological tests

APPENDIX I Préliminary study

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PART I

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Commissariat à l'Energie Atomique
France

September 1977

ABSTRACT

A pharmacokinetic study of the metabolism of MDI in rats was carried out using MDI labelled with ^{14}C, with a specific activity of 24,7 mCi/mM. The radiochemical purity of the compound was checked.

The animals were contaminated via the respiratory tract.

The most salient results of this investigation are the following :

- the fecal elimination of MDI and its metabolites is greater than urinary elimination
- after four days 70 % of the absorbed dose are eliminated
- bile secretion in free flow during the 46,5 first hours following contamination via the respiratory tract corresponds to 5 % of the dose received by the animal
- MDI (^{14}C) is distributed fairly uniformly throughout the organism, with a predominance for the lungs, muscle, liver, kidneys and the digestive tract.

- histological tests performed on lung fragments led to the observation of :
  - congestion of capillaries
  - desquamation and destruction of bronchial epithelium
  - constriction of bronchi up to obstruction

INTRODUCTION

The purpose of this work was to investigate the diffusion rate of MDI in the organi of rats contamined via the respiratory tract.

The study was carried out on a group of 12 male rats. Contamination took place i specially built sealed enclosure under controlled atmosphere.

This work follows a preliminary study intended to estimate the diffusion rate of MD blood after intramuscular injection (Appendix I). These results were a perequis before undertaking contamination via the respiratory tract, which requires the use large-scale equipment.

The work covered by this report includes the following :

(1) A study of the kinetics of distribution of MDI in the organism, by the mea rement of total radioactivity after respiratory contamination. The follow were determined :

- rate of fecal and urinary excretions
- distribution in :
  - blood
  - bile
- distribution of ^{14}C in the different organs.

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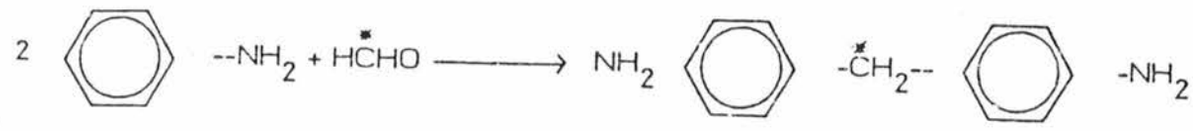
SYNTHESIS OF THE MOLECULE

The MDI (^{14}C) was synthesized by the Laboratoire des Molécules Marquées of th Commissariat à l'Energie Atomique at Saclay.

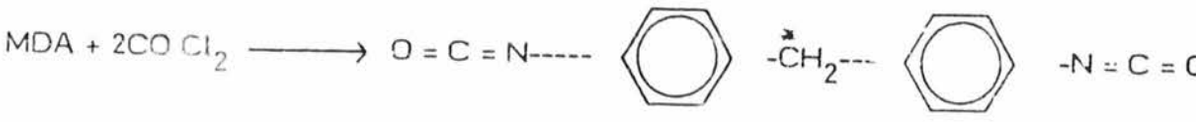
(a) Synthesis

The following scheme was followed for synthesis of the labelled compound.

1) Formol condensation with aniline to give MDA



2) To obtain MDI, crude MDA is treated by $COCL_2$



b) Purification and tests

MDA was purified by chromatography on a column of "Silice H". Thin layer chromatography and UV tritation are used as tests of the purification (fig. 1 and 2). This pure MDA is used to ended the synthesis of MDI. The results of radiochemical controls appear on figure 3 and 4.

The final product has a radioactivity of 24,7 mCi/mM.

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PART 2

PHARMACOKINETIC STUDY

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1 EQUIPMENT AND METHODS

1.1 Biological material

The animal used was the adult male rat of the Sprague Dawley strain (Charles Rive with an average weight of 300 ± 10 g.

1.2 Technique of contamination by inhalation

Special equipment for studies of radioactive contamination by the respiratory tra belonging to the Département de Protection of the Commissariat à l'Energ Atomique, was used.

The installation includes an inhalation chamber in which the animals are placed fo contamination.

The product under study is suspended in the atmosphere of the enclosure by means of generator. The whole system was placed in a second gastight enclosure (glovebox). Th generator (Figure 5), based on the technique of Lauterbach, Hayes and Coelho+, i designed to produce an aerosol with droplets of reproductible particle size distribution Its flow rate matches the normal respiratory rate of the animals. It utilizes compressed dry air jet under high pressure and at low flow rate (1.4 bar through three holes 0.3 mm in diameter, giving a flow rate of 3.5 l/min) flush with the surface of the liquid to be put in suspension.

+K.E. Lauterbach, A.B. Hayes and M.A. Coelho : An improved aerosol generator, Archs Ind. Health, 13, 156 (1956).

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The resulting aerosol is very dense and consists of drops of different sizes. The bigges drops are retained by the tubular half-tore connecting the generator to the inhalatio enclosure. The maximum diameter of the drops which are not retained is 5 μ.

The individual restraining cages containing the animals (a total of 12 rats) were place in the inhalation chamber which has a volume of 5 liters. The rats were no anesthetized. The truncated-cone shape of the cephalic extremity of their restrainin recipient and the small size of this recipient limited external contamination of th animal to its muzzle. In general, rats decontaminate their fur themselves in two o three days.

The exposure chamber was kept under slight vacuum in relation to the glovebox, whic features independent atmospheric flushing. The tightness of the system was ensured b a set of rings and gaskets.

The rats were exposed with the labelled compound for 15 minutes in these experimental conditions. Two millicuries were introduced in the generator (specific activity 24,7 mCi/mM or 20,250 mg of MDI (^{14}C).

Remarks

A control performed on the bottom of the generator shows that most of the radioactivity remained in it at the end of the contamination period. Since the vapor tension of MDI is very low at room temperature (18-20°C), only the solvent and part of the MDI were suspended in the atmosphere. It is thus impossible to calculate MDI concentration in the inhalation chamber.

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1.3 Radioactivity measurement by liquid scintillation

The radioactivity from ^{14}C was measured by means of an Intertechnique (SL 32 P liquid scintillation spectrometer. The samples were prepared by mineralizati (Intertechnique IN 4101 unit). The results were corrected for quenching and in functi of the specific efficiency of the counting instrument.

The scintillating solution had the following composition :

toluene	400 ml
phenylethylamine	330 ml
methyl alcohol	220 ml
PPO	7 g
bis MSB	0.4 g
water	20 ml

1.4 Evaluation of results

The results reported in this study correspond to measurements of the total radioac tivity due to ^{14}C in the samples. They are evaluated in each case as a fraction of the total radioactivity received by each animal. The tables listing the means also give the standard error of these means, as well as the number of experiments performed.

2 EXPERIMENTAL PROCEDURES

All the results mentioned here were obtained from animals contaminated simultaneously.

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2.1 Variation in radioactivity concentration in the blood and plasma

The radioactivity in the blood of animals used for dissections of organs was measure on an aliquot of the whole blood obtained by puncture of the abdominal aorta at th time the animals were killed.

An aliquot of plasma obtained after centrifugation of whole blood was also mineralize for radioactivity measurement. Two groups of animals were used, the first group kille immediately after contamination, the second 24 hours after. This second set of rat was used for several experimental procedures. (see table I).

Concentration in plasma

The blood of animals was centrifuged to obtain plasma. The plasma was put in a ultrafiltration cone with a membrane having a separating power of 25,000 (centriflo amicon system type CF 25). The radioactivity of the ultrafiltrate obtained was determined by liquid scintillation. No more than 30 % of the plasma volume used for ultrafiltration is filtered through the membrane.

2.2 Excretion balance of radioactivity

In order to obtain the excretion balances of MDI and its metabolic ..ivatives, the animals were kept individually in glass metabolism cages (Figure 6) designed to obtain separate collection of urine and faeces. Aside from the 12 hours before and 3 hours after contamination by MDI, the animals received water and powdered food.

The urines and faeces were collected during the periods of 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72 and 72 to 96 hours after administration of the MDI (^{14}C), and the samples corresponding to each period were stored in the freezer while awaiting treatment. 200 microli..ers of urine were directly mineralized in the IN 4101 unit. The

feces were oven-dried to constant weight, powdered, and an aliquot of each samp mineralized with 10 microliters of isobutyl alcohol. The latter was used to facilita combustion of the sample.

Respiratory tract

During the experimental period the amount of expired $^{14}CO_2$ is followed. The cage are ventilated with air at a rate of 330 ml/min. At the outlet of the cage, a pump i used to collect 10 % of the circulating air, which bubles in two flasks connected i series and contain an alkaline solution (phenylethylamine) (fig.6).

The animals were killed at the end of the experiment. The carcass of each animal wa homogenized in the presence of a quantity of water equal to its weight. Th radioactivity of the homogenate was measured.

2.3 Bile secretion of radioactivity

One rat weighing 300 g was anesthetized with 5 % nembutal using 0.1 ml per gram o body weight. The common bile duct was catheterized and the end of the cathe'e slipped under the skin to make it emerge in the back of the animal. The rat was then placed in a restraining cage and kept warm. The free flowing bile was collected in a fraction collector over periods of 1½ hours. The bile secreted during each period was weighed and the radioactivity measured on aliquots of 100 microliters. The experiment was pursued as long as permitted by the condition of the animal.

2.4 Autoradiography of the whole animal

One 300 g rat contaminated via the respiratory tract with MDI (^{14}C) was killed 15 minutes after treatment and rapidly frozen by immersion in liquid nitrogen. The frozen rat was stored for at least 24 hours in a freezer at -25°C before preparation of the

slices to be used for autoradiographies slices were prepared according to Ullberg technique (1954)+ modified by Cohen and Delassus (1959)+. A Leitz microtome wa used with a plate cooled to -30°C.

60 μ sections parallel to the sagittal axis of the animal were prepared and collected o an adhesive strip. After dehydration they were placed on a Kodirex single-coa radiological Kodak film. The films were developed after 6 days of exposure. The blac areas enable localization of the radioactivity caused by the ^{14}C introduced into th body of the animal as MDI (^{14}C).

2.3 Distribution in the organs

The rats were anesthetized and bled by puncture of the abdominal aorta. The animals were then dissected and the following organs removed :

- brain
- heart
- stomach
- liver
- large intestine
- small intestine
- muscles
- eyes
- skin
- lungs
- spleen
- kidneys
- adrenals
- testicles
- thyroid

and the whole blood, plasma and ultrafiltrable.

The contents of the digestive tract was also collected.

+Ullberg S, Acta Radiol. Supp., 118 (1954).

+Cohen Y., Delassus H., C.R. Soc. Biol. 153, p.300-305 (1959).

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After dissection the organs were rapidly washed with a squirt of saline, to remove a adhering blood, dried rapidly by dabbing with absorbent paper.

The small organs (less than 0.6 g) were put into weighed cellulose acetate capsul fitted with covers. After weighing, the samples were burnt in their dishes in order prepare the sample for radioactivity measurement by liquid scintillation.

The larger organs were placed in tared glass containers. After weighing, a knov quantity of distilled water was added prior to homogeneization. An aliquot of t homogenate was mineralized for radioactivity measurement by liquid scintillation.

Animals were killed for dissection 0.25, 24, 72 and 96 hours after the end of t contamination period.

Two males were dissected for each period. The individual doses they accumulated a listed in the tables of results.

The results are evaluated as follows :

1) The radioactivity found in each organ is calculated as a fraction of the accumulat dose x 10^{-5}.

2) This value, when divided by the weight of the organ, gives the concentration radioactivity per gram of organ.

Tests on the animal

A serie of 12 animals corresponded to the experimental procedure defined collaboration wih the International Isocyanates Institute. Table I summarizes t following for each of these 12 rats :

- the period after which the animal was killed following the end of contaminati
- data gathered for each anim.l

Table II indicates the individual doses received by each animal, assuming that thes doses can be expressed as unconverted MDI (^{14}C).

2.6 Histological tests

Lung samples were used for histological investigation.

Fixation dehydration

After washing with saline, the lung sample was immersed into a Bouin-Holland solution (picric acid + formol + acetic acid + copper acetate) for a few days. The lung was then washed under running water, and then dehydrated in ethanol of increasing alcoholic content up to absolute alcohol.

Inclusion in paraffin

As ethanol is immiscible with paraffin, the lung sample was soaked in toluene to eliminate ethanol before impregnation with paraffin. This impregnation was carried out in an oven at 60°C, and was facilitated by passages under vacuum.
The samples were then cast in paraffin blocks.

Section

The block was cut into 5 μ sections with a Jung or Spencer microtome.

Staining

Staining was performed with Masson's Hemalun, erythrosin and safran.

3 RESULTS

3.1 Variation in radioactivity in the blood and plasma

Table III gives the individual results of variations in radioactivity in the blood, and t plasma for rats contaminated via the respiratory tract with MDI (^{14}C). Table indicates the means corresponding to each period at the end of which the animals we killed and bled. The curves in Figures 7 and 8 illustrate the results of Table IV. Figure 7 the concentration of radioactivity in the blood and plasma are plotted as function of time in linear coordinates. The disappearance of radioactivity occurs in th same manner in whole blood and in the plasma. The concentration of radioactivity the plasma remained greater than in whole blood during these experiments.

In Figu 8 a semi-logarithmic scale is used to plot the concentrations of radioactivit in blood and plasma as a function of time. These curves show that, within the exper mental errors, the elimination of MDI (^{14}C) and of its metabolites from the bloo follows a multicompartimental distribution.

3.2 Urinary and fecal excretion of radioactivity

Table V gives the individual results of fractions of radioactivity eliminated during each sampling period. These same results are used in Table VI which allows to follow the cumulated excretion of MDI (^{14}C) or its derivatives as a function of time.

The curve in Figure 9 illustrates the results given in Table VI. These results show that expired air contains about 2 % of $^{14}CO_2$ (table VI B).

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To summarize, these experiments show the following :

- that the fecal elimination of MDI (^{14}C) and it metabolites labelled with ^{14}C i greater than their urinary elimination (57 % as compared with 13 %)
- that the excreta recovery balance is better than 70 %. 23 % of the administered radioactivity are found in the carcass after the animals are killed.

Summary

Elimination of MDI and its metabolites by the faeces is more important than by the urine.

After four days 70 % of the absorbed dose is eliminated.

3.3 Bile secretion of radioactivity

These results were obtained with a single rat.

The cumulated amounts of ^{14}C secreted in the bile as a function of time are shown in Table VII.

The curve in Figure 10 illustrates the variation as a function of time of the importance of biliary secretion. It shows that the cumulative amount excreted by the liver in 46,5 hours is about 5 % of the total radioactivity absorbed by the animal.

The results in Table VIII make it possible to compile the radioactivity balances found in the excreta and the body of the rat examined. Note that 7,8 % of the radioactivity was eliminated by the urines, 5 % by the bile, and 7,6 % by the faeces. A large fraction of

the radioactivity is found in the carcass (79 %) at the time the animal was killed.

Summary

5 % of the radioactivity due to MDI (^{14}C) and its metabolites is eliminated b the bile.

The peak of radioactivity in the bile occurs between the 6th and 9th hours.

3.4 Autoradiography of the whole animal

Plates I and II show the autoradiography of rats killed 15 minutes and 24 hours afte contamination by the respiratory tract with MDI (^{14}C).

This result was obtained for the selected period after 1 month of contact of the section with the film. The relative importance of tissue fixation appears in table IX.

The autoradiography in plates I and II show that the radioactivity appears to be localized at the respiratory tract, the stomach, small intestine and the large intestine.

Summary

Slight labelling of the respiratory tract, stomach, small and large intestine.

3.5 Distribution in the organs

All the results are shown in tables X to XX. These tables give the results radioactivity measurements in these organs at the moment the animals were killed, t fraction of the total dose injected found in the organs, as well as the concentrati factor. Tables X and XI give the means calculated from the various individual resu in tables XII to XX.

The localizations of radioactivity observed in the autoradiographies of whole anima were confirmed and quantified by these results. Among the most noteworthy, it shou be observed that aside from the contents of the digestive tract (stomach and sma intestine), the highest concentrations occured in the lungs, the muscles and the liver. The considerable labelling of the digestive tract contents is probably explainable b the fact that during contamination via the lungs, the animals ingurgitate and thu swallow a fairly large fraction of the labelled product.

Summary

The most strongly labelled organs are the muscles, kidneys, liver.

3.6 Histological tests

Histological examination of slices of lungs from rats contaminated with MDI (^{14}C) lead to the following observations :

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- presence of many polynuclear cells
- diffuse infiltration by mononuclear cells
- presence of numerous lymphocytes
- proliferation of pneumocytes II
- congestion of capillaries
- destruction of bronchial epithelium and desquamation

Summary

Congestion of capillaries

Destruction of bronchial epithelium and desquamation

constriction of bronchi up to obstruction

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TABLE I

Summary table of data gathered on each animal after contamination via the respiratory tract with MDI (^{14}C)

Rat number	period in hours	
1,2	0.75	- radioactivity in the blood, plasma, ultrafiltrable - distribution in organs - residual radioactivity in the body - histological test of a lung fragment
3,4	24	- radioactivity in the blood, plasma, ultrafiltrable - radioactivity excreted by urines and faeces - distribution in organs - residual radioactivity in the body - histological test of a lung fragment
5,6	72	- radioactivity in the blood, plasma, ultrafiltrable - radioactivity excreted by urines and faeces - distribution in organs - residual radioactivity in the body - histological test of a lung fragment
7,8,9	96	- urinary and fecal excretion balance - radioactivity in the blood, plasma, ultrafiltrable - distribution in organs - residual radioactivity in the body
10	46.5	- bile secretion - radioactivity excreted in the urine and faeces - residual radioactivity in the body
11,12	0.75	- autoradiography of the whole animal

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Rat n°	1	2	3	4	5	6	7	8	9	10	11	12
Weight in g.	315	335	335	320	330	335	325	340	325	310	335	315
Dose received by the animal ng	0.0238	0.0133	0.0202	0.0260	0.0176	0.0148	0.0137	0.0127	0.0167	0.0185	-	-

Table II : Individual doses evaluated as MDI (^{14}C) received by the animals. These doses are computed from the total radioactivit accumulated by each animal (calculated by adding the radioactivity eliminated to that remaining in the body of the animal at tl end of the experiment), and assuming that 1 ng of unconverted MDI (^{14}C) corresponds to 13712168 desintegrations per minute.

Period in hours	rat n°	Total Blood	Plasma
0,25	1	1.4550	1.9799
	2	1.7178	2.1062
24	3	0.7793	1.2628
	4	0.6166	0.9109
72	5	0.4307	0.7662
	6	0.6394	0.8361
96	7	0.5333	0.6258
	8	0.5011	0.5827

Table III : individual results showing the variation as a function of time in ^{14}C radioactivity concentration in the blood, plasma and ultrafiltrable fraction of the plasma, in rats contaminated via the respiratory tract with MDI (^{14}C). The results are evaluated as a function of the total radioactivity received by each rat, calculated per gram of blood, plasma or ultrafiltrable.

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Period in hours	Total blood		Plasma	
0.25	1.5864	(2)	2.0431	(2)
24	0.6980	(2)	1.0869	(2)
72	0.5351	(2)	0.8012	(2)
96	0.5172	(2)	0.6043	(2)

Table IV : Disappearance of ^{14}C radioactivity in the blood and plasma of rats contaminated by the respiratory tract with TDI (^{14}C).

Results are evaluated in parts per 1000 per gram of total radioactivity administered.

The means given in this table were obtained from the individual results appearing in Table III. The figure in parentheses indicates the number of animals used in calculating the means.

Although the experimental conditions were slightly different, the results of both series of experiments served in calculating the means.

N°	7	8	9	
Sex	♂	♂	♂	
Dose administered	0.0422	0.0374	0.0514	Mean ± es
Weight in g.	325	340	325	
Period h				
URINES				
0 - 6	35.59	51.05	27.21	37.95 ± 6.98
6 - 12	15.70	39.16	41.16	32.01 ± 8.17
12 - 24	12.52	16.83	17.42	15.59 ± 1.54
24 - 48	18.21	29.35	19.79	22.45 ± 3.48
48 - 72	12.71	10.42	10.87	11.33 ± 0.70
72 - 96	7.53	9.86	19.09	12.16 ± 3.53
Total	102.26	156.67	135.54	131.49 ± 15.84
FAECES				
0 - 6	0	0	2.12	0.71
6 - 12	0	0	1.38	0.46
12 - 24	133.93	219.76	299.32	217.67 ± 47.76
24 - 48	299.37	203.53	150.93	191.61 ± 20.91
48 - 72	140.52	65.13	72.78	92.81 ± 23.96
72 - 96	63.26	65.99	72.34	67.20 ± 2.69
Total	558.08	554.41	598.87	570.45 ± 14.25
Total Urines + Faeces	660.34	711.08	734.41	701.94 ± 21.86
Carcass	234.52	211.42	247.03	230.99 ± 10.43

Table V : Individual results showing urinary and fecal elimination of ^{14}C as a function of time, after respiratory contamination with MDI (^{14}C). The results are expressed in parts per 1000 of the dose administered. The mean for each period was calculated. The symbol 0 denotes the absence of faeces.

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N°	7	8	9			
Sex	♂	♂	♂			
Dose administered	0.0422	0.0374	0.0514	Mean	±	es
Weight in g.	325	340	325			
Period h						
URINES						
0 - 6	35.59	51.05	27.21	37.95	±	6.98
6 - 12	51.29	90.21	68.37	69.96	±	11.26
12 - 24	63.81	107.04	85.79	85.55	±	12.48
24 - 48	82.02	136.39	105.58	108.00	±	15.74
48 - 72	94.73	146.81	116.45	119.33	±	15.10
72 - 96	102.26	156.67	135.54	131.49	±	15.84
FAECES						
0 - 6	0	0	2.12	0.71		
6 - 12	0	0	3.50	1.17		
12 - 24	133.93	219.76	302.82	218.84	±	48.76
24 - 48	354.30	423.29	453.75	410.45	±	29.42
48 - 72	494.82	488.42	526.53	526.53	±	11.78
72 - 96	553.08	554.41	598.87	570.45	±	14.25

Table VI : Individuel results showing the cumulative urinary and fecal elimination of ^{14}C as a function of time, in rats after respiratory contamination with MDI (^{14}C).

The results are expressed in parts per 1000 of the dose administered. The mean for each period was calculated. The symbol 0 denotes the absence of faeces.

N° Sex	7 ♂	8 ♂	9 ♂	Mean ± es
Period h				
0 - 6	2.7016	3.8390	3.1730	3.2379 ± 0.3299
6 - 12	2.4080	3.5872	5.2403	3.7452 ± 0.8214
12 - 24	4.5223	2.8320	3.7019	3.6854 ± 0.4880
24 - 48	2.9953	2.8320	3.2692	3.0322 ± 0.1275
48 - 72	1.8207	2.3915	1.5384	1.9169 ± 0.2509
72 - 96	4.4636	2.6432	1.6346	2.9138 ± 0.8278
Total	18.9114	18.1249	18.5574	18.5312 ± 0.2274

Table VI B : Fraction of the cumulative dose absorbed, eliminated as a function of time by the respiratory tract. The results are expressed in parts per 1000 of the dose administered.

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Period h	°/oo	°/oo cumul.	°/oo/g^{-1}
0 - 1.5	3.4437	3.4437	25.0026
1.5 - 3	-	-	-
3 - 4.5	-	-	-
4.5 - 6	0.8491	4.2928	1.3759
6 - 7.5	0.4364	4.7292	1.6511
7.5 - 9	3.4477	8.1769	1.6708
9 - 10.5	2.9327	11.1096	1.4939
10.5 - 12	2.4649	13.5745	1.2776
12 - 13.5	2.2251	15.7996	1.1990
13.5 - 15	2.3509	18.1505	1.1990
15 - 16.5	2.3234	20.4739	1.1597
16.5 - 18	2.2487	22.7226	1.1204
18 - 19.5	2.0953	24.8179	1.0418
19.5 - 21	2.0206	26.8385	1.0221
21 - 22.5	1.9106	28.7491	1.1007
22.5 - 24	1.9656	30.7147	1.0418
24 - 25.5	1.9342	32.6489	1.3563
25.5 - 27	1.7573	34.4062	1.1401
27 - 28.5	1.5489	35.9551	1.0418
28.5 - 30	1.6786	37.6337	1.1204
30 - 31.5	1.6865	39.3202	1.0811
31.5 - 33	1.8870	41.2072	1.2894
33 - 34.5	1.4899	42.6971	1.1007
34.5 - 36	1.3720	44.0691	1.0221
36 - 37.5	1.4034	45.4725	1.0025
37.5 - 39	1.4231	46.8956	1.1007
39 - 40.5	1.3327	48.2283	1.2187
40.5 - 42	1.2698	49.4981	1.2383
42 - 43.5	1.4585	50.9566	1.5921
43.5 - 45	1.1007	52.0573	1.3956
45 - 46.5	0.9631	53.0204	1.5253

Table VII : Individual results showing the biliary elimination and cumulative biliary elimination of ^{14}C in a rat contaminated via the respiratory tract with MDI (^{14}C). The results are calculated as a fraction of the total radioactivity received by the rat.

RAT N°	CUMULATIVE BILE	CARCASS %	URINE %	FAECES %	WEIGHT OF DRIED FAECES IN GRAM
10	5.7	79.0	7.8	7.6	1.04

Table VIII : Bile excretion balance of MDI and its metabolites labelled with ^{14}C in a rat contaminated via the respiratory tract.
The results are calculated as a function par 100 of the total radioactivity detected in the different elements after 46.5 hours.
The fraction found in the carcass corresponds to the total radioactivity present in the carcass at the moment it was killed.

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Time in hours	0,25	24
ORGANS	Intensity of blackening	
LARYNX	+	
LUNGS	++	++
STOMACH	+++	++
SMALL INTESTINE	++	
LARGE INTESTINE		++

Table IX : Amount of radioactivity localized by autoradiography in rats contaminated by the respiratory tract with MDI (^{14}C) for 0,25 and 24 hours.

+++	Strong
++	Medium
+	Weak

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SUMMARY OF RESULTS

RADIOACTIVITY DISTRIBUTION (MEANS)

Organs	0.25 hour	24 hours	72 hours	96 hours
Number of rats	2	2	2	2
BRAIN	0.3897	0.2615	0.2395	1.5608
HEART	0.4179	0.2949	0.3426	0.4894
CONT.DIG.TRACT.	80.9788	56.4006	16.4952	14.5159
STOMACH	1.9653	0.6052	0.3972	0.4112
LIVER	11.5013	6.1720	4.1219	4.4165
LARGE INTESTINE	1.2521	1.2075	0.7073	1.3258
SMALL INTESTINE	7.5180	1.3203	0.9239	1.7069
MUSCLES	69.6523	26.1781	24.9542	63.7886
EYE	0.6137	0.1355	0.1215	0.0585
SKIN	13.0155	10.2553	10.2611	9.3406
PLASMA	31.8612	16.7148	13.1368	9.2906
LUNGS	77.5560	34.4184	39.0911	26.5157
SPLEEN	0.2624	0.1465	0.1499	0.1187
KIDNEYS	5.2693	1.1560	0.6478	1.0188
WHOLE BLOOD	44.2972	19.6421	15.2686	14.7279
ADRENALS	0.0299	0.0343	0.0193	0.0440
TESTICLES	0.9683	0.7735	0.4949	0.6285
THYROID	0.0373	0.0433	0.0428	0.0630
ULTRAFILTRABLE	2.3383	1.6460	1.8204	1.6616

Table X :Fraction of the total dose absorbed as a function of time in the different organs (x 10^{-3}).

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SUMMARY OF RESULTS

DISTRIBUTION OF RADIOACTIVITY/WEIGHT (MEANS)

Organs	0.25 hour	24 hours	72 hours	96 hours
Number of rats	2	2	2	2
BRAIN	0.2411	0.1818	0.1524	0.4979
HEART	0.4278	0.2974	0.3428	0.4951
CONT.DIG.TRACT.	5.9589	3.7094	0.9368	1.2571
STOMACH	1.5755	0.4289	0.2875	0.3567
LIVER	1.0366	0.4469	0.2699	0.3195
LARGE INTESTINE	0.7241	0.6789	0.3345	0.9404
SMALL INTESTINE	1.7048	0.3298	0.1945	0.5291
MUSCLES	0.5207	0.1729	0.1636	0.4189
EYE	2.4671	0.5518	0.4747	1.1125
SKIN	0.7253	0.5689	0.5638	0.5134
PLASMA	2.0431	1.0869	0.8012	0.6043
LUNGS	61.7278	26.8822	25.9160	16.1895
SPLEEN	0.3332	0.2134	0.1688	0.1685
KIDNEYS	2.3074	0.5135	0.2731	0.4216
WHOLE BLOOD	1.5864	0.6980	0.5351	0.5172
ADRENALS	0.6829	0.9419	0.5005	0.8807
TESTICLES	0.2934	0.2414	0.1489	0.2083
THYROID	2.7065	4.0493	2.8128	2.5749
ULTRAFILTRABLE	0.1495	0.1082	0.1114	0.1098

Table XI : Concentration factor (radioactivity/gram) of different organs for ^{14}C absorbed by the animals ($\times 10^{-3}$).

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EXPERIMENTAL DATA

Tables XII to XX : Individual results of the study of the distribution of radioactivity in the organs of rats contaminated via the respiratory tract with MDI (^{14}C).

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EXPERIMENTAL DATA

rat n°	1
product	MDI
duration of experiment	0.25h
hematocrit	0.43
number of DPM absorbed by the animal	325 777
sex	♂
weight of the animal	315 grams

RESULTS ON THIS RAT

Organs	weight of organ	organ radioactivity	radioactivity distr.	radioactivity /weight
BRAIN	1.4286	36	0.1105	0.0773
HEART	0.9094	96	0.2948	0.3242
CONT.DIG.TRACT.	11.5260	21345	65.5214	5.6847
STOMACH	1.1231	547	1.6788	1.4948
LIVER	10.4964	3757	11.5255	1.0980
LARGE INTESTINE	1.6757	380	1.1660	0.6958
SMALL INTESTINE	4.0538	2770	8.5015	2.0972
MUSCLES	143.9353	12399	38.0598	0.2644
EYE	0.2460	227	0.6968	2.8325
SKIN	17.5686	3801	11.6687	0.6642
PLASMA	15.3874	9925	30.4652	1.9799
LUNGS	1.1784	24271	74.5019	63.2229
SPLEEN	0.6630	64	0.1965	0.2963
KIDNEYS	2.1196	1005	3.0860	1.4559
WHOLE BLOOD	26.9955	12796	39.2780	1.4550
ADRENALS	0.3900	7	0.2150	0.5510
TESTICLES	3.0693	165	0.5066	0.1651
THYROID	0.0150	10	0.0307	2.0464
ULTRAFILTRABLE	15.3874	538	1.6532	0.1074

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EXPERIMENTAL DATA

rat n°	2
product	MDI
duration of experiment	0.25h
hematocrit	0.45
number of DPM absorbed by the animal	182 795
sex	♂
weight of the animal	335 grams

RESULTS ON THIS RAT

Organs	weight of organ	organ radio-activity	radioactivity distr.	radioactivity /weight
BRAIN	1.6531	122	0.6693	0.4048
HEART	1.0182	99	0.5410	0.5313
CONT.DIG.TRACT.	15.4719	17628	96.4362	6.2330
STOMACH	1.3596	412	2.2517	1.6561
LIVER	11.7696	2098	11.4770	0.9751
LARGE INTESTINE	1.7785	245	1.3381	0.7524
SMALL INTESTINE	4.9792	1194	6.5344	1.3123
MUSCLES	154.3303	18507	101.2447	0.7770
EYE	0.2525	97	0.5306	2.1016
SKIN	18.2634	2625	14.3623	0.7864
PLASMA	15.7902	6079	33.2571	2.1062
LUNGS	1.3383	14735	80.6101	60.2327
SPLEEN	0.8870	60	0.3282	0.3701
KIDNEYS	2.3592	1362	7.4525	3.1589
WHOLE BLOOD	28.7095	9015	49.3164	1.7178
ADRENALS	0.0470	7	0.0383	0.8148
TESTICLES	3.3919	261	1.4299	0.4216
THYROID	0.0130	8	0.0438	3.3665
ULTRAFILTRABLE	15.7902	553	3.0234	0.1915

EXPERIMENTAL DATA

rat n°	3
product	MDI
duration of experiment	24 h
hematocrit	0.45
number of DPM absorbed by the animal	277 167
sex	♂
weight of the animal	335 grams

RESULTS ON THIS RAT

Organs	weight of organ	organ radio-activity	radioacti-vity distr.	radioactivity /weight
BRAIN	1.3311	98	0.3529	0.2651
HEART	0.9599	90	0.3259	0.3395
CONT.DIG.TRACT.	13.7554	20495	73.9433	5.3756
STOMACH	1.3832	228	0.8223	0.5945
LIVER	13.0108	1945	7.0180	0.5394
LARGE INTESTINE	1.8837	447	1.6129	0.8562
SMALL INTESTINE	3.8806	467	1.6853	0.4343
MUSCLES	154.3303	8766	31.6271	0.2049
EYE	0.2400	51	0.1840	0.7667
SKIN	18.2634	3140	11.3290	0.6203
PLASMA	15.7902	5527	19.9395	1.2628
LUNGS	1.2418	11574	41.7582	33.6272
SPLEEN	0.6640	47	0.1696	0.2554
KIDNEYS	2.2635	370	1.3350	0.5898
WHOLE BLOOD	28.7095	6201	22.3737	0.7793
ADRENALS	0.0350	12	0.0433	1.2370
TESTICLES	3.2278	256	0.9254	0.2867
THYROID	0.0110	17	0.0613	5.5759
ULTRAFILTRABLE	15.7902	395	1.4242	0.0902

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EXPERIMENTAL DATA

rat n°	4
product	MDI
duration of experiment	24 h
hematocrit	0.46
number of DPM absorbed by the animal	356 777
sex	♂
weight of the animal	320 grams

RESULTS ON THIS RAT

Organs	weight of organ	organ radioactivity	radioactivity distr.	radioactivity /weight
BRAIN	1.7280	61	0.1701	0.0985
HEART	1.0339	94	0.2639	0.2552
CONT.DIG.TRACT.	19.0178	13864	38.8579	2.0432
STOMACH	1.4743	138	0.3881	0.2632
LIVER	15.0295	1900	5.3260	0.3544
LARGE INTESTINE	1.5988	286	0.8020	0.5016
SMALL INTESTINE	4.2409	341	0.9552	0.2252
MUSCLES	146.5200	7360	20.6291	0.1408
EYE	0.2580	31	0.0869	0.3368
SKIN	17.7438	3276	9.1816	0.5175
PLASMA	14.8090	4813	13.4900	0.9109
LUNGS	1.3347	9361	27.0785	20.1372
SPLEEN	0.7200	44	0.1233	0.1713
KIDNEYS	2.2353	349	0.9769	0.4371
WHOLE BLOOD	27.4240	6033	16.9105	0.6166
ADRENALS	0.0390	9	0.0252	0.6468
TESTICLES	3.1707	222	0.6216	0.1961
THYROID	0.0100	9	0.0000	0.0025
ULTRAFILTRABLE	14.8090	666	1.8678	0.1261

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EXPERIMENTAL DATA

rat n°	5
product	MDI
duration of experiment	72 h
hematocrit	0.43
number of DPM absorbed by the animal	241 448
sex	♂
weight of the animal	330 grams

RESULTS ON THIS RAT

Organs	weight of organ	organ radio-activity	radioacti-vity distr.	radioactivity /weight
BRAIN	1.3955	33	0.1359	0.0974
HEART	0.9989	84	0.3474	0.3478
CONT.DIG.TRACT.	17.8207	2626	0.8777	0.6104
STOMACH	1.2478	60	0.2474	0.1983
LIVER	15.2989	858	3.5553	0.2324
LARGE INTESTINE	2.1063	165	0.6816	0.3236
SMALL INTESTINE	4.9441	189	0.7830	0.1584
MUSCLES	151.7175	4644	19.2340	0.1284
EYE	0.2530	42	0.1740	0.6876
SKIN	18.0911	1816	7.5217	0.4158
PLASMA	16.1202	2982	12.3515	0.7662
LUNGS	1.2814	6741	27.9191	21.7872
SPLEEN	0.8410	32	0.1325	0.1576
KIDNEYS	2.4364	148	0.6113	0.2509
WHOLE BLOOD	28.2810	2941	12.1816	0.4307
ADRENALS	0.0350	1	0.0041	0.1183
TESTICLES	3.2000	132	0.5454	0.1704
THYROID	0.0160	4	0.0166	1.0354
ULTRAFILTRABLE	16.1202	484	2.0029	0.1243

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EXPERIMENTAL DATA

rat n°	6
product	MDI
duration of experiment	72 h
hematocrit	0.42
number of DPM absorbed by the animal	203 330
sex	♂
weight of the animal	335 grams

RESULTS ON THIS RAT

Organs	weight of organ	organ radio-activity	radioacti-vity distr.	radioactivity /weight
BRAIN	1.6535	70	0.3430	0.2074
HEART	0.9798	67	0.3309	0.3377
CONT.DIG.TRACT.	17.5047	4496	22.1127	1.2632
STOMACH	1.4522	111	0.5470	0.3767
LIVER	15.2565	953	4.6885	0.3073
LARGE INTESTINE	2.1223	149	0.7329	0.3453
SMALL INTESTINE	4.6194	216	1.0647	0.2305
MUSCLES	154.3303	6237	30.6743	0.1988
EYE	0.2630	14	0.0689	0.2618
SKIN	18.2634	2643	13.0005	0.7118
PLASMA	16.6515	2831	13.9220	0.8361
LUNGS	1.6730	10220	50.2631	30.0448
SPLEEN	0.9290	34	0.1672	0.1800
KIDNEYS	2.3168	139	0.6842	0.2953
WHOLE BLOOD	28.7095	3732	18.3556	0.6394
ADRENALS	0.0390	7	0.0344	0.8827
TESTICLES	3.4899	90	0.4444	0.1273
THYROID	0.0150	14	0.0689	4.5902
ULTRAFILTRABLE	16.6515	333	1.6379	0.0984

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EXPERIMENTAL DATA

rat n°	7
product	MDI
duration of experiment	96 h
hematocrit	0.46
number of DPM absorbed by the al	187 294
sex	♂
weight of the animal	325 grams

RESULTS ON THIS RAT

Organs	weight of organ	organ radio-activity	radioacti-vity distr.	radioactivity /weight
BRAIN	1.3934	112	0.6101	0.4378
HEART	0.9079	98	0.5306	0.5845
CONT.DIG.TRACT.	11.7445	3815	20.7592	1.7676
STOMACH	1.1571	110	0.5982	0.5170
LIVER	13.0302	901	4.9039	0.3764
LARGE INTESTINE	1.4037	320	1.7396	1.2393
SMALL INTESTINE	3.4925	326	1.7746	0.5081
MUSCLES	149.1141	15135	82.3665	0.5497
EYE	0.2263	14	0.0762	0.3367
SKIN	17.9180	1579	8.5951	0.4797
PLASMA	15.0404	1730	9.4129	0.6258
LUNGS	1.6297	4874	26.5249	16.2774
SPLEEN	0.7077	19	0.1034	0.1461
KIDNEYS	2.3546	207	1.1270	0.4786
WHOLE BLOOD	27.8525	2730	14.8545	0.5333
ADRENALS	0.0518	14	0.0762	1.4708
TESTICLES	2.9335	149	0.8117	0.2767
THYROID	0.0225	21	0.1143	5.0793
ULTRAFILTRABLE	15.0404	526	2.8648	0.1905

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EXPERIMENTAL DATA

rat n°	8
product	MDI
duration of experiment	96 h
hematocrit	0.46
number of DPM absorbed by the animal	174 787
sex	♂
weight of the animal	340 grams

RESULTS ON THIS RAT

Organs	weight of organ	organ radioactivity	radioactivity distr.	radioactivity /weight
BRAIN	1.7038			
HEART	1.1048			
CONT.DIG.TRACT.	11.0821	77	0.4481	0.4056
STOMACH	1.1413	1420	8.2725	0.7465
LIVER	14.9608	38	0.2242	0.1964
LARGE INTESTINE	1.4220	674	3.9291	0.2626
SMALL INTESTINE	2.9800	157	0.9120	0.6414
MUSCLES	156.9525	281	1.6392	0.5501
EYE	0.1655	7759	45.2106	0.2881
SKIN	18.4346	2	0.0117	0.0704
PLASMA	15.7345	1731	10.0860	0.5471
LUNGS	1.6463	1573	9.1683	0.5827
SPLEEN	0.7020	4559	26.5064	16.1016
KIDNEYS	2.4978	23	0.1340	0.1909
WHOLE BLOOD	29.1380	156	0.9105	0.3645
ADRENALS	0.0401	2506	14.6013	0.5011
TESTICLES	3.1826	2	0.0117	0.2906
THYROID	0.0216	76	0.4452	0.1399
ULTRAFILTRABLE	15.7345	7	0.0408	1.8883
		79	0.4584	0.0291

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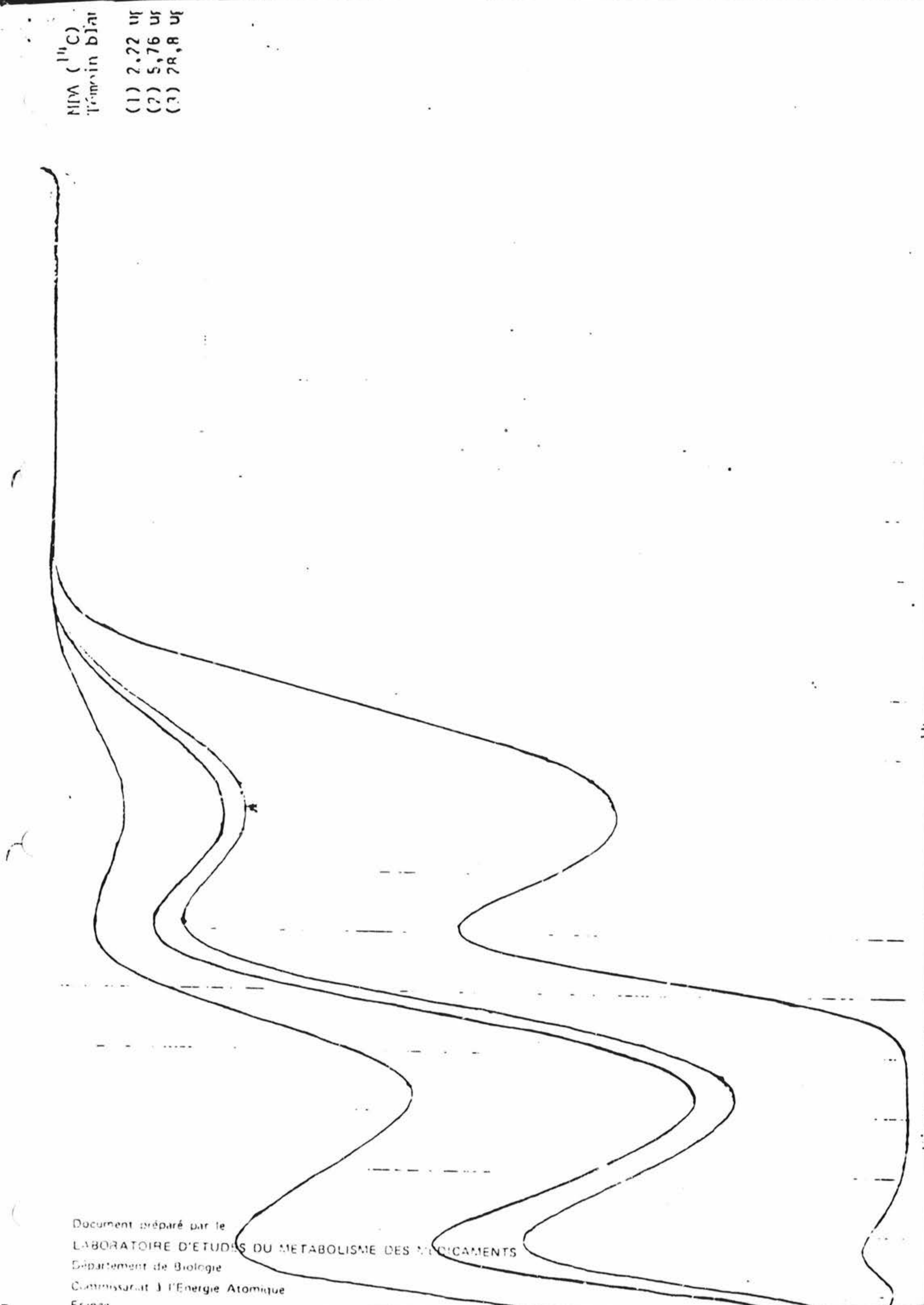

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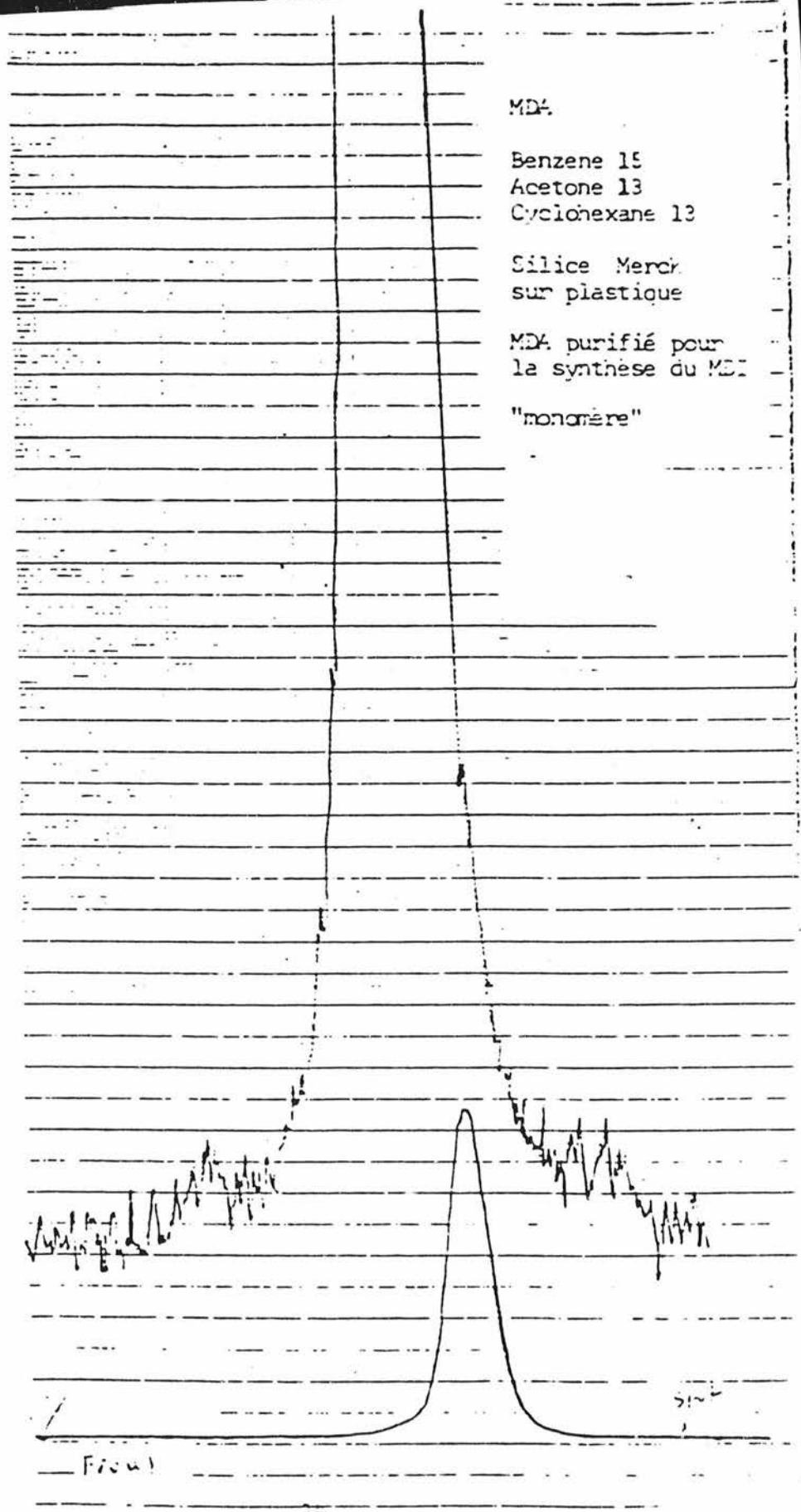

Figure 2 : Radio chemical control of MDA (^{14}C). The chromatography has been developp with the system of solvent : Benzene 15
Acetone 13
Cyclohexane 13

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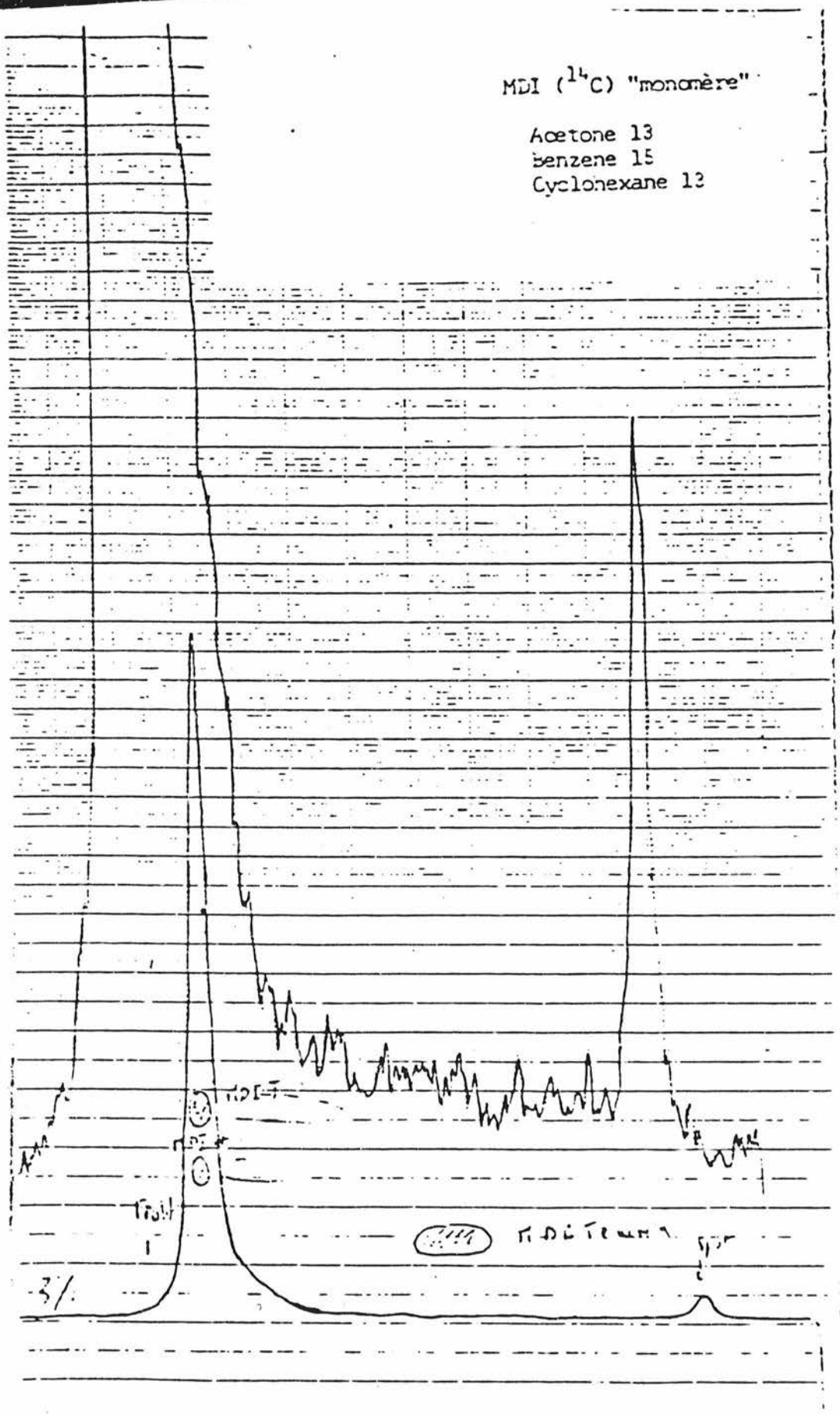

Figure 3 : Radio chemical control of MDI (^{14}C) "monomeride". The chromatography has been developp with the system of solvent : Benzene 15
Acetone 13
Cyclohexane 13

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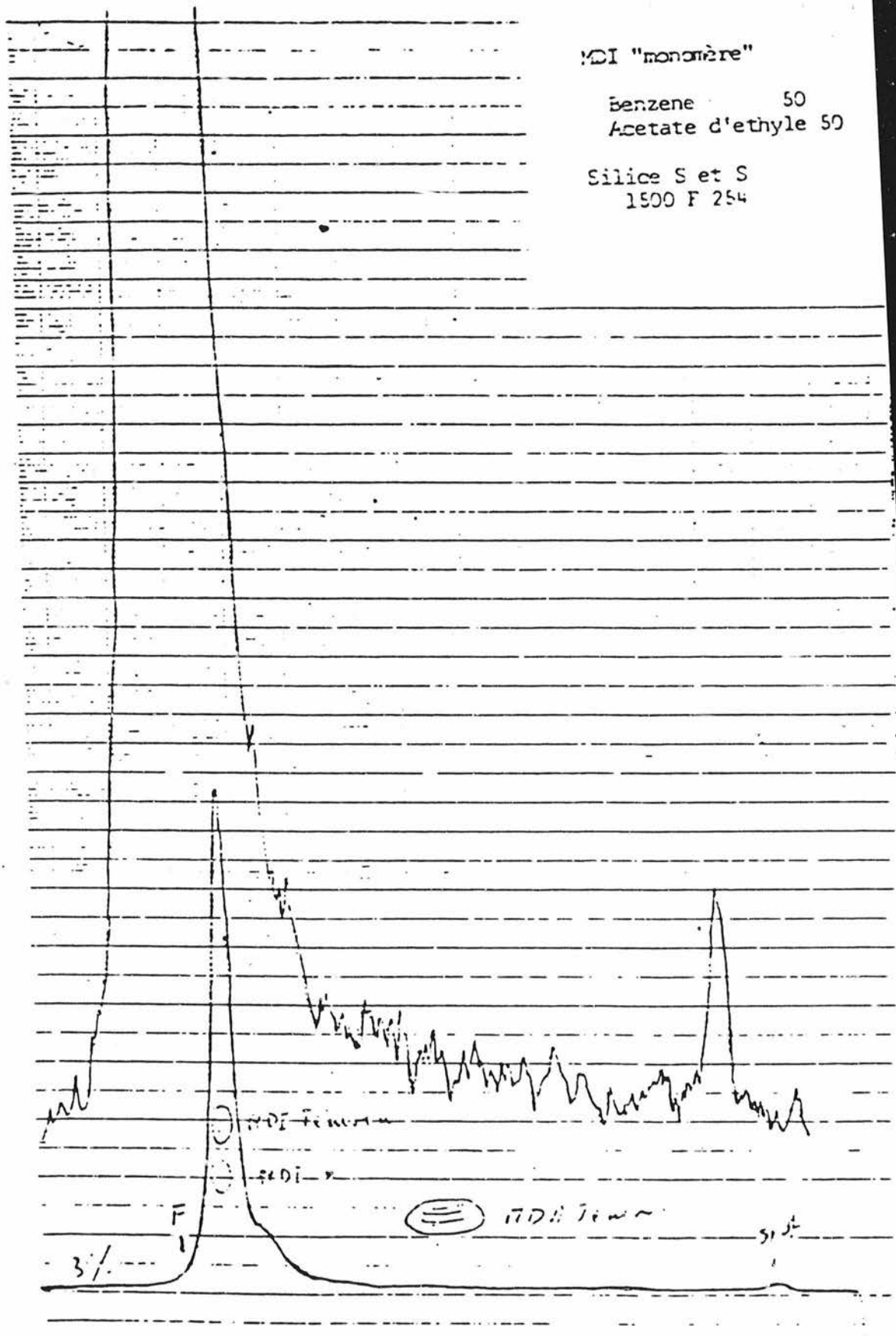

Figure 4 : Radio chemical control of MDI (^{14}C) "monomeride". The chromatography has been developp with the system of solvent : Benzene 50
Acetate d'ethyle 50

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Figure 5 : Detail of aerosol generator

1. compressed air
2. adjustable height tube
3. O-rings
4. semi-circular tube
5. aerosol
6. extremity of tube
7. lateral hole 0.3 mm
8. solution to be suspension
9. O-ring
10. removable bottom
11. to enclosure

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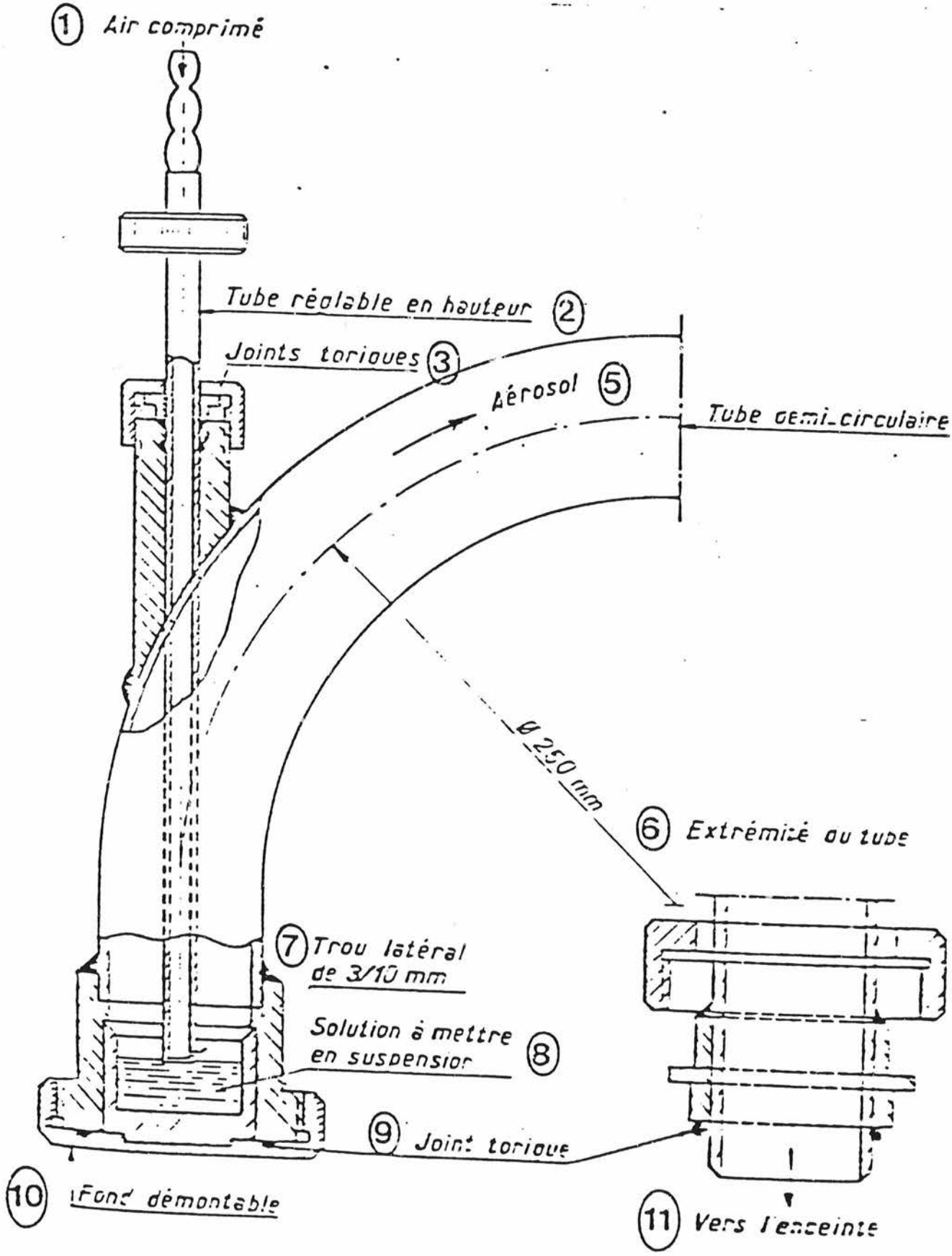

FIG 5 _DETAIL DU GENERATEUR D'AEROSOL

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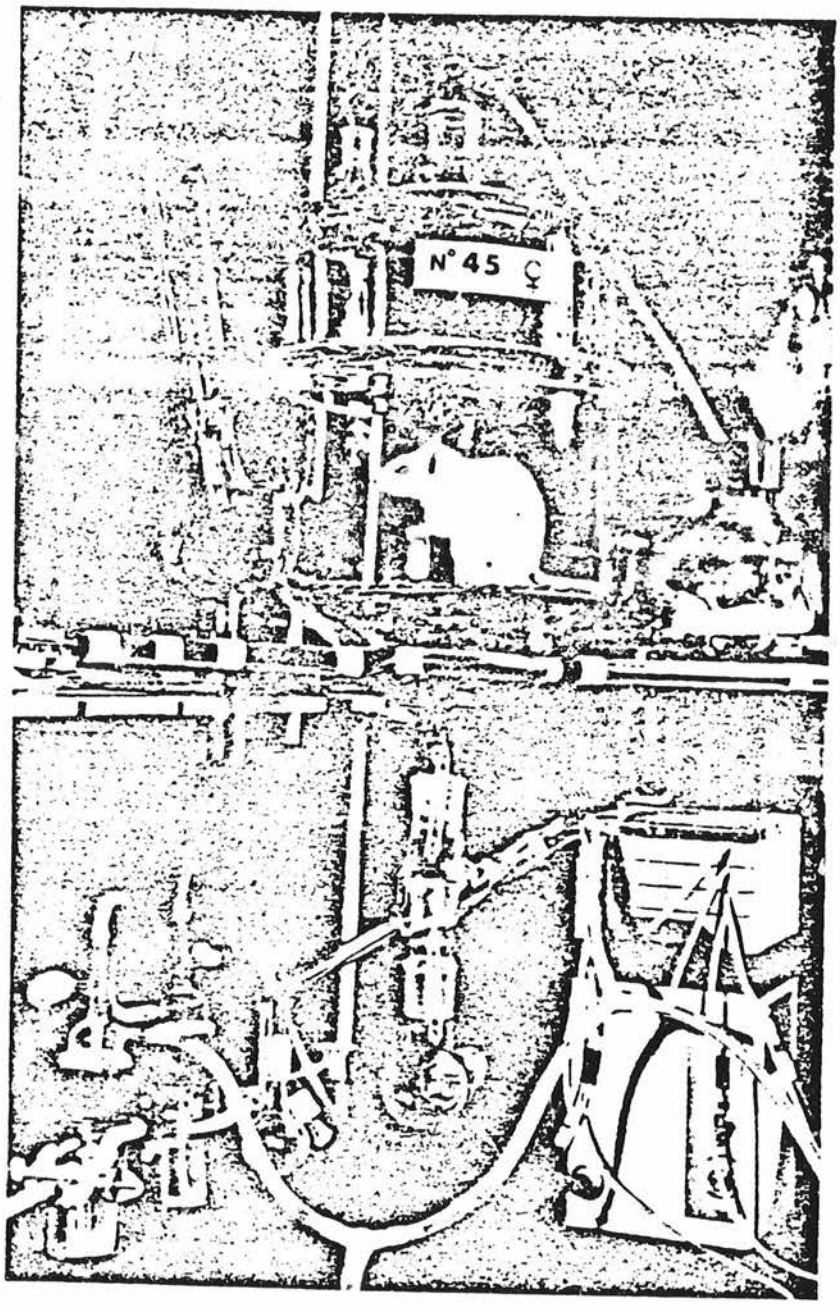

Figure 6 : Cage used for metabolic studies of MDI. The urines and faeces are collected separately in flasks located below the cage.

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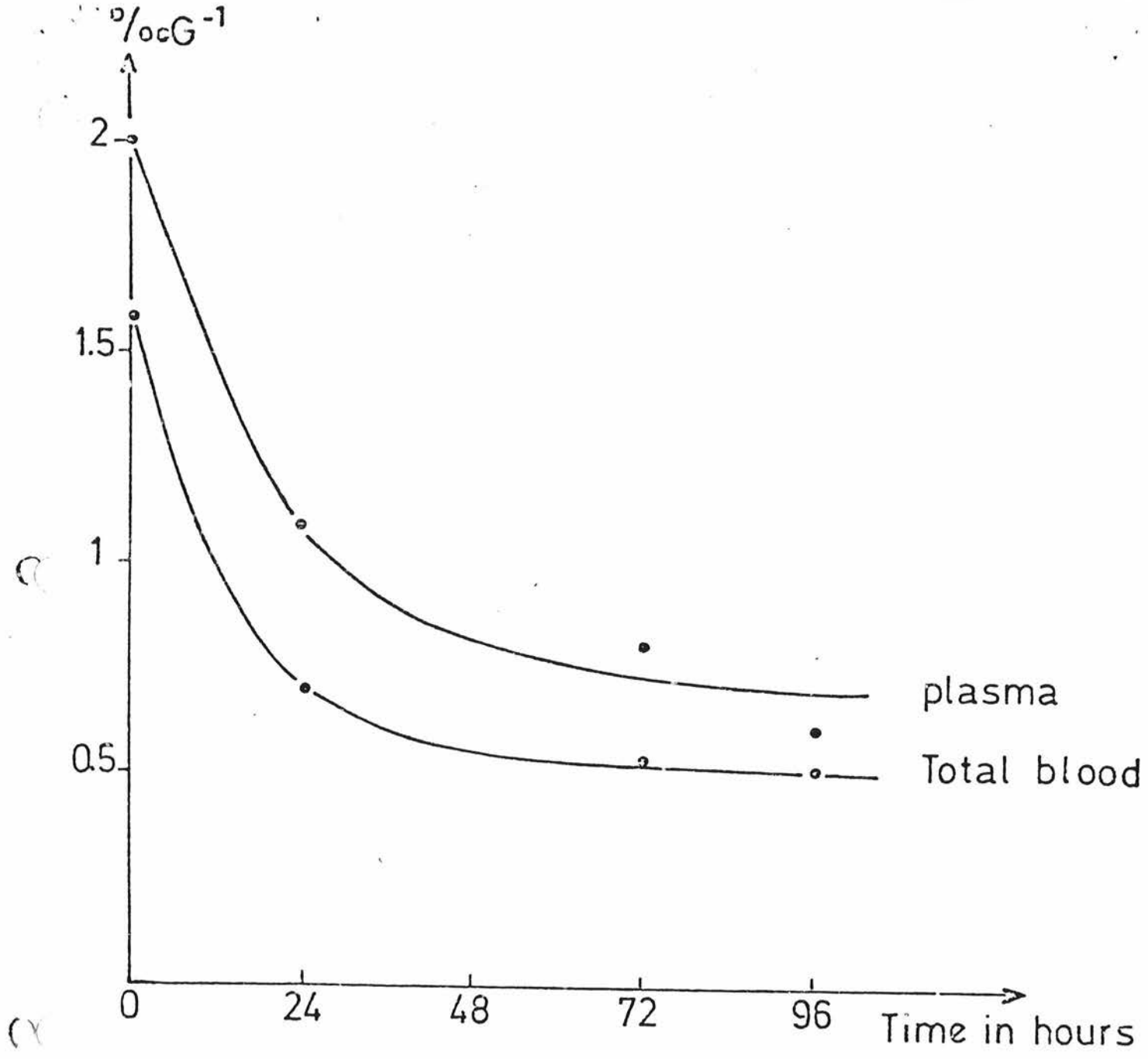

Figure 7 : Variation as a function of time of the concentration of ^{14}C radioactivity in the blood and the plasma of rats after respiratory contamination with MDI (^{14}C).

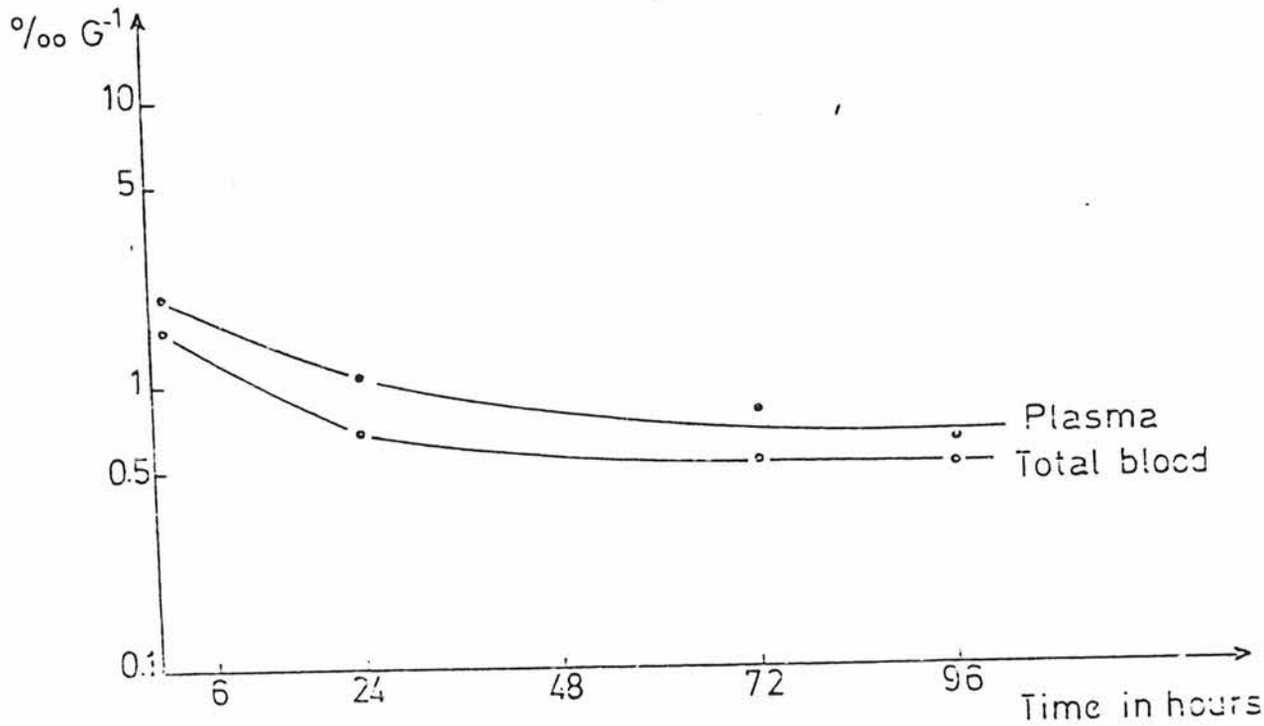

Figure 8 : Variation as a function of time of the logarithm of radioactivity in the bloo and the plasma contaminated by the respiratory tract with MDI (^{14}C). This curve wa plotted using the results in table IV.

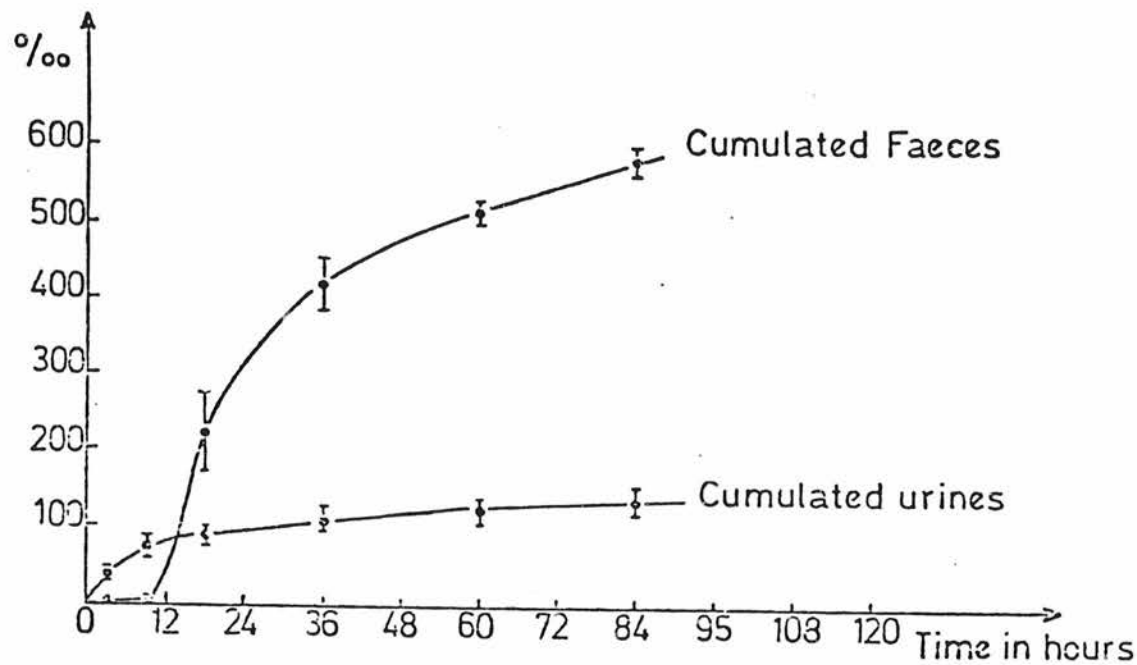

Figure 9 : Variation as a function of time of ^{14}C radioactivity eliminated in the urines and faeces in rats contaminated via the respiratory tract with MDI (^{14}C).

This curve was plotted using the results given in table VI.

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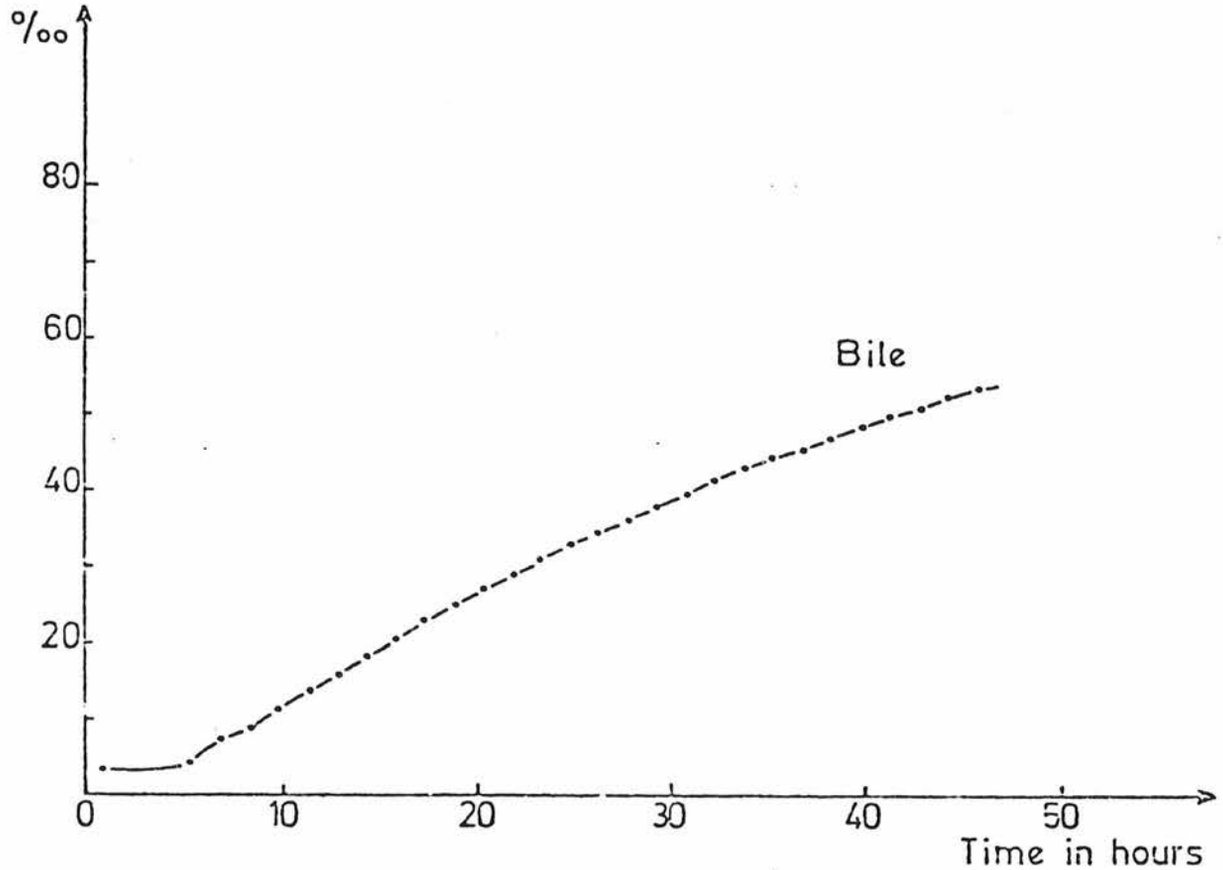

Figure 10 : Variation as a function of time of cumulative radioactivity of the bile secreted by a male rat previously contaminated via the respiratory tract with MDI (^{14}C).

This curve was plotted from the results in table VIII.

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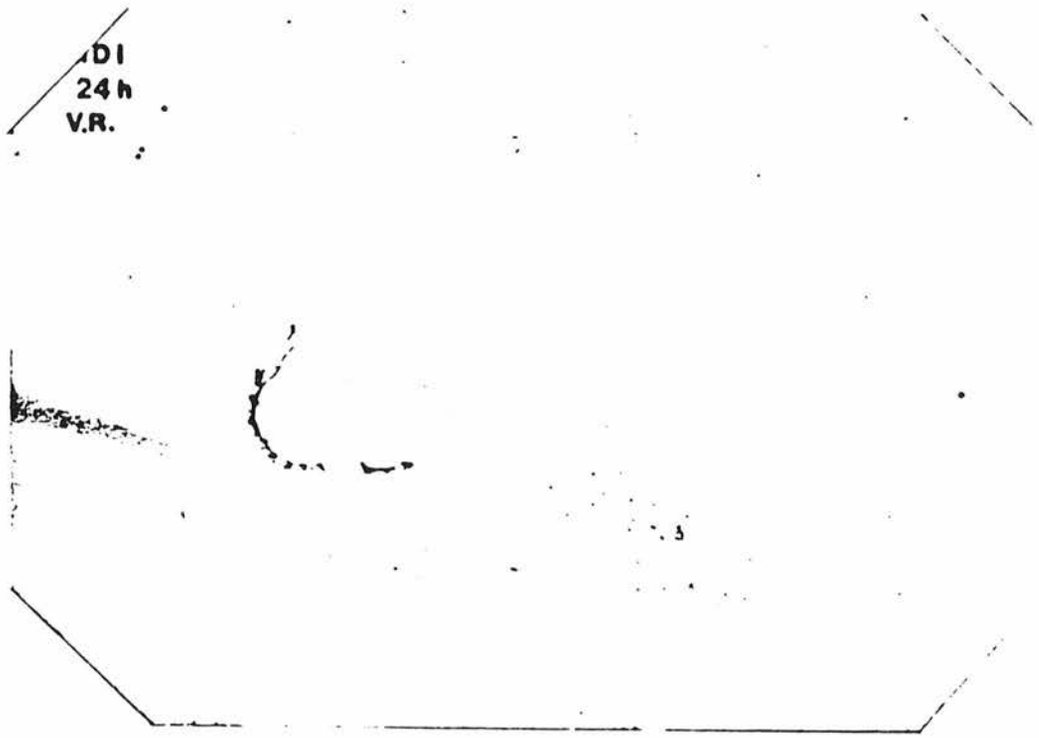
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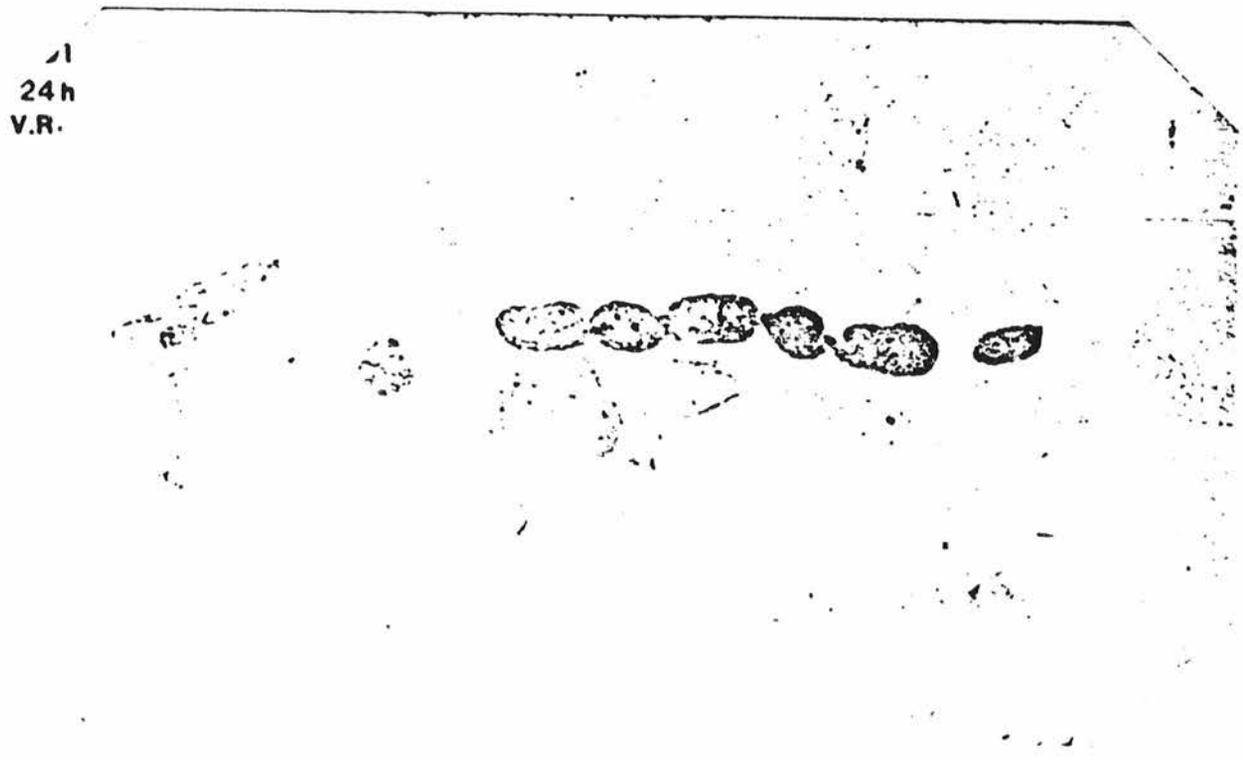
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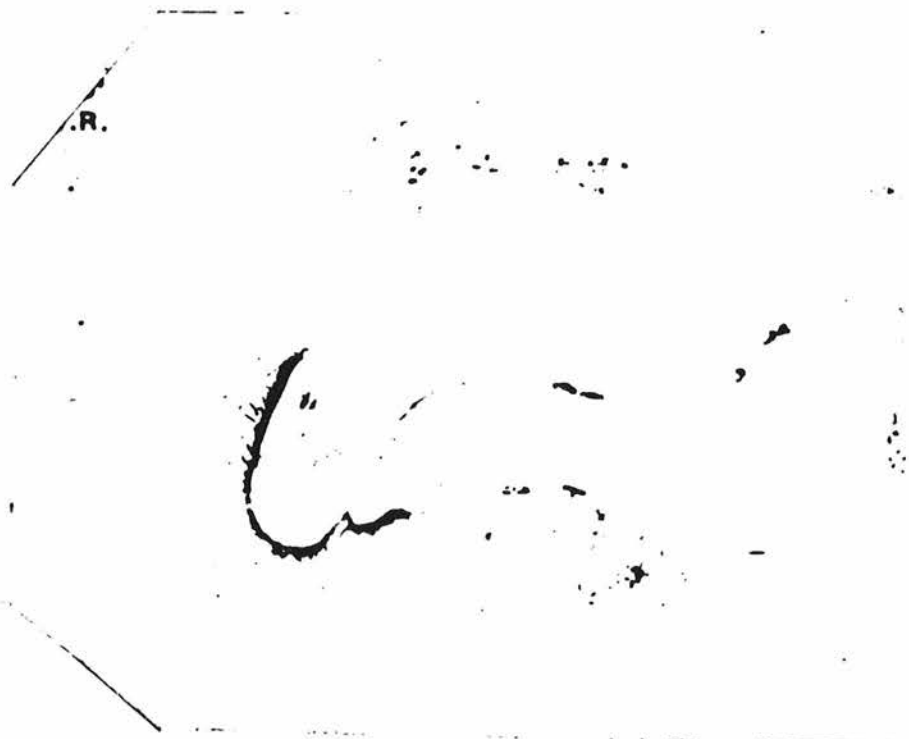
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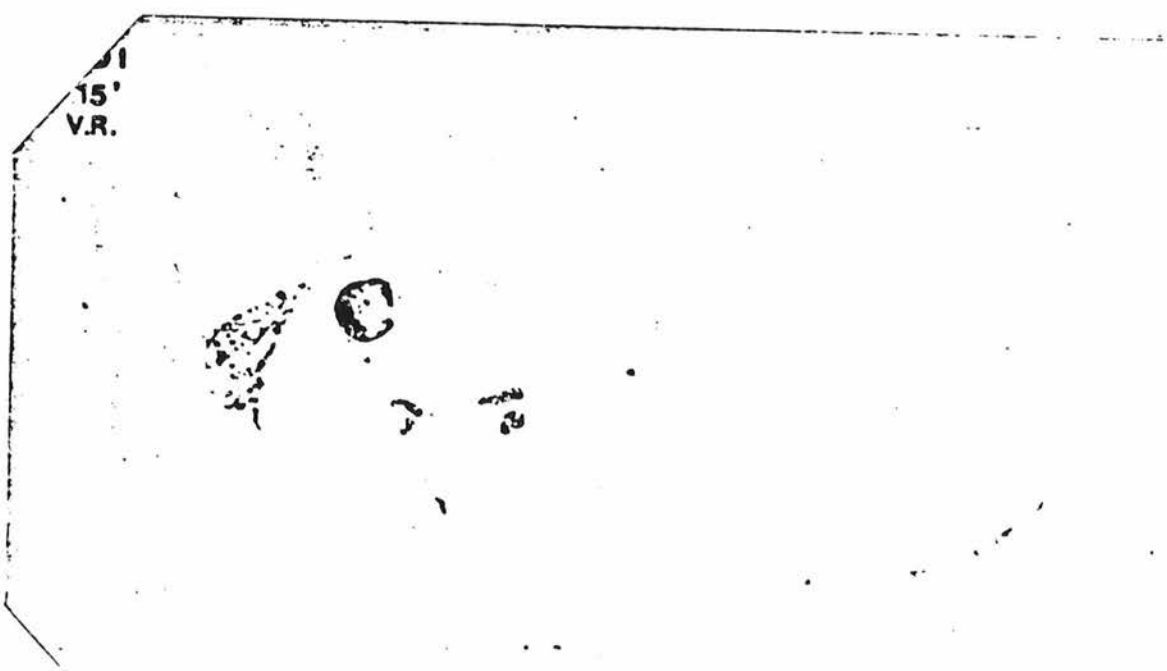
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